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- (71) Applicant (for all designated States except US): **DAN-IOLABS LIMITED** [GB/GB]; 7330 Cambridge Research Park, Landbeach, Cambridge, Cambridgeshire CB5 9TN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **GOLDSMITH, Paul** [GB/GB]; 7330 Cambridge Research Park, Landbeach, Cambridge, Cambridgeshire CB5 9TN (GB). **FLEMING, Angeleen, Louise** [GB/GB]; 7330 Cambridge Research Park, Landbeach, Cambridge, Cambridgeshire CB5 9TN (GB). **RICHARDS, Andrew, John, McGlashan** [GB/GB]; 7330 Cambridge Research Park, Landbeach, Cambridge, Cambridgeshire CB5 9TN (GB). **JONES, Derek, Thomas, Edward** [GB/GB]; 7330 Cambridge Research Park, Landbeach, Cambridge, Cambridgeshire CB5 9TN (GB). **HARRIS, William, Anthony** [CA/GB]; 7330 Cambridge Research Park, Landbeach, Cambridge, Cambridgeshire CB5 9TN (GB).
- (74) Agents: **WALTON, Seán, M. et al.**; Mewburn Ellis, York House, 23 Kingsway, London, Greater London WC2B 6HP (GB).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: FISH DISEASE MODELS AND USES THEREOF

(57) Abstract: Generation and use of disease models, for instance in assays to identify and investigate genes and substances involved in disease and disease treatment, identification and use of drug targets. In particular, the present invention relates to generation and use of disease models in fish such as zebrafish. Gradable phenotypes may be generated in fish, allowing for degree of correction or alteration of an activity or effect of a treatment, gene or mutation to be assayed. Competing stimuli may be applied to fish in screens assaying for ability to affect an activity or effect of a treatment, gene or mutation. Example include any combination of an addictive drug, a visual stimulus, an audible startle stimulus, a temperature gradient, an electric shock, an aversive compound, a threatening shape or a dark area.

INTERNATIONAL SEARCH REPORT

GB 03/05239

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/50 A61K49/00 A01K67/027 C12Q11/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N A61K A01K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SERBEDZIJA G N ET AL: "Zebrafish angiogenesis: a new model for drug screening." ANGIOGENESIS. 1999, vol. 3, no. 4, 1999, pages 353-359, XP002272288 ISSN: 0969-6970 the whole document	1, 2, 25, 30, 36
X	WO 02/18594 A (HUH TAE LIN ; PARK HAE CHUL (KR); KIM CHUL HEE (KR); KIM HYUNG SEOK (K) 7 March 2002 (2002-03-07) the whole document ----- -/--	1, 2, 25, 30, 36

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

3 March 2004

Date of mailing of the international search report

03.08.04

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seransk1, P

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>LANGHEINRICH ULRIKE: "Zebrafish: a new model on the pharmaceutical catwalk." BIOESSAYS : NEWS AND REVIEWS IN MOLECULAR, CELLULAR AND DEVELOPMENTAL BIOLOGY. SEP 2003, vol. 25, no. 9, September 2003 (2003-09), pages 904-912, XP002272289 ISSN: 0265-9247 the whole document</p>	1,2,25, 30,36
Y	<p>PETERSON R T ET AL: "Small molecule developmental screens reveal the logic and timing of vertebrate development" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 24, 21 November 2000 (2000-11-21), pages 12965-12969, XP002233342 ISSN: 0027-8424 the whole document</p>	1-22, 25-42
Y	<p>WO 98/56902 A (LIN SHUO ; MEDICAL COLLEGE OF GEORGIA RES (US)) 17 December 1998 (1998-12-17) the whole document</p>	1-22, 25-42
Y	<p>WO 01/40273 A (UCKUN FATIH M ; PARKER HUGHES INST (US)) 7 June 2001 (2001-06-07) the whole document</p>	1,25-29, 30-42
Y	<p>WO 00/32822 A (SERBEDZIJA GEORGE N ; SEMINO CARLOS E (US); MCGRATH PATRICIA (US); PHY) 8 June 2000 (2000-06-08) the whole document</p>	1,2,25, 29,30, 35,36-42
Y	<p>BAIER H: "ZEBRAFISH ON THE MOVE: TOWARDS A BEHAVIOR-GENETIC ANALYSIS OF VERTEBRATE VISION" CURRENT OPINION IN NEUROBIOLOGY, LONDON, GB, vol. 10, no. 4, August 2000 (2000-08), pages 451-455, XP001150387 ISSN: 0959-4388 the whole document</p>	1-22, 25-42
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INTERNATIONAL SEARCH REPORT

PCT/GB 03/05239

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>KENNEDY B N ET AL: "Isolation of a zebrafish rod opsin promoter to generate a transgenic zebrafish line expressing enhanced green fluorescent protein in rod photoreceptors"</p> <p>JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 276, no. 17, 27 April 2001 (2001-04-27), pages 14037-14043, XP002238860 ISSN: 0021-9258 the whole document</p>	12,12,15
Y	<p>DARLAND T ET AL: "Behavioral screening for cocaine sensitivity in mutagenized zebrafish."</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. 25 SEP 2001, vol. 98, no. 20, 25 September 2001 (2001-09-25), pages 11691-11696, XP002272290 ISSN: 0027-8424 the whole document</p>	3,4

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 17, 21 (complete), 18-20, 22 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-21, 22 (partially), 25-42

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention1: Claims 1-21, 22 (partially), 25-42

Methods for screening for a substance or gene using zebrafish.

Inventions 2: Claims 22(partially), 23-24

Method for determining effect of a substance on a fish the method comprising applying the substance dissolved in dimethyl sulphoxide (DMSO) to water inhabited by fish.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 17, 21 (complete), 18-20, 22 (partially)

Present claims 17-22 relate to an extremely large number of possible compounds. No support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found for such compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 03/05239

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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